TRIAL STATISTICAL ANALYSIS PLAN

c39759578-01

BI Trial No.:	1479-0003
Title:	Relative bioavailability of BI 1810631 as two different oral formulations given as single doses and investigation of the effects of food and multiple-dose rabeprazole on the pharmacokinetics of single-dose BI 1810631 following oral administration in healthy male subjects (an open-label, randomised, four-way crossover trial)
Investigational Product(s):	BI 1810631
Responsible trial statistician(s):	[redacted] Phone: [redacted]
Date of statistical analysis plan:	17 OCT 2022 SIGNED
Version:	1

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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine transaminase
ANOVA	Analysis of variance
AST	Aspartate transaminase
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
BMI	Body mass index
BP	Blood Pressure
CDR	Clinical Data Repository
CI	Confidence interval
CL	Confidence interval limit
C_{max}	Maximum measured concentration of the analyte in plasma
CSD	Company Standard Displays
CV	Arithmetic coefficient of variation
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDMS	Electronic Document Management System
F/U	Follow Up
gCV	Geometric coefficient of variation
gMean	Geometric mean
iCF	Intended Commercial Formulation
iPD	Important Protocol Deviation
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
N	Number non-missing observations
NF	New formulation
P10	10^{th} percentile
P90	90^{th} percentile
PD	Protocol deviation
PKS	PK parameter analysis set
PR	Pulse Rate
PT	Preferred Term
Q1	1^{st} quartile

Term	Definition / description
Q3	3rd quartile
qd	Quaque die
R	Reference treatment
RAGe	Report Appendix Generator system
REP	Residual Effect Period
RPM	Report Planning Meeting
SD	Standard deviation
SOC	System organ class
T	Test treatment
TS	Treated set
t_z	Time of last measurable concentration of the analyte in plasma
WHO-DD	World Health Organization Drug Dictionary

3. INTRODUCTION

As per ICH E9 (1), the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This TSAP assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 "Statistical Methods and Determination of Sample Size". Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomization.

Study data as collected in the eCRF will be stored in a trial database within the RAVE EDC system. All study data also including external data will then be uploaded to the CDR data warehouse.

Pharmacokinetic (PK) parameters will be calculated using [redacted] software (version 8.1.1 or higher, [redacted]) or [redacted] Version 9.4 (or later version).

The statistical analyses will be performed within the validated working environment CARE, including [redacted] (current Version 9.4, by [redacted]), and a number of [redacted] (e.g., macros for the analyses of AE data or laboratory data; [redacted] for compilation/formatting of the CTR appendices).

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

All analyses as planned in the CTP will be performed and are described in more detail in this TSAP.

5. ENDPOINTS(S)

5.1 PRIMARY ENDPOINT(S)

Section 2.1.2 of the CTP:

The following pharmacokinetic parameters will be determined for BI 1810631:

- *AUC0-tz (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point)*
- *Cmax (maximum measured concentration of the analyte in plasma)*

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

This section is not applicable as no key secondary endpoints have been defined in the CTP.

5.2.2 Secondary endpoint(s)

Section 2.1.3 of the CTP:

The following pharmacokinetic parameter will be determined for BI 1810631:

- $AUC_{0-\infty}$ *(area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)*

[redacted]

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For basic study information on investigational products and selection of doses, please see CTP Sections 3 and 4.

For details of dosage and formulations see Table 6.1: 1 below.

Table 6.1:1 Treatments and labels used in the analysis

Treatment	Label	Short label
TF1 fasted (R)	[redacted] BI 1810631 TF1 on Day 1 under fasting condition	TF1-fast
NF fasted (T1)	[redacted] BI 1810631 NF on Day 1 under fasting condition	NF-fast
NF fed (T2)	[redacted] BI 1810631 NF on Day 1 under fed condition	NF-fed
NF fasted + rabeprazole (T3)	[redacted] BI 1810631 NF on Day 1 under fasting condition and 2 tablets of 20 mg rabeprazole sodium q.d. on Days -4 to 1	Rabeprazole (Day -4 to Day 1) AND NF-fast+Rab. (after administration of BI on Day 1)

The subjects were randomly allocated to the 4 treatment sequences:

1. "TF1 fasted"-"NF fasted"-"NF fed"-"NF fasted + rabeprazole" (R – T1 – T2 – T3)
2. "NF fasted"-"NF fasted + rabeprazole"-"TF1 fasted"-"NF fed" (T1 – T3 – R – T2)
3. "NF fed"-"TF1 fasted"-"NF fasted + rabeprazole"-"NF fasted" (T2 – R – T3 – T1)
4. "NF fasted + rabeprazole"-"NF fed"-"NF fasted"-"TF1 fasted" (T3 – T2 – T1 – R)

Section 1.2.3 of the CTP:

[redacted]

The REP of rabeprazole [redacted]

[redacted]

Table 6.1:2 Analysis phases for statistical analysis of AEs

Study analysis phase	Label	Start	End
Screening[1]	Screening	Date of informed consent	Date/time of first administration of BI drug or rabeprazole
On treatment	Rabeprazole (only for T3)	Date/time of first administration of rabeprazole	Date/time of first administration of BI drug OR Date/time of the last administration of rabeprazole + 3 days of REP, whichever occurs first.
	TF1-fast, NF-fast, NF-fed, NF-fast+Rab., respectively	Date/time of administration of BI drug in the respective treatment period	Date/time of administration of BI drug in the respective treatment period + residual effect period [redacted] OR Date/time of first administration of rabeprazole OR 12:00 a.m. on day after last contact date (whichever occurs first)
Follow-up	F/U	Date/time of administration of BI drug + [redacted]	Date/time of (first) administration of study drug in the next treatment period, if applicable OR Date/time of trial termination (12:00 a m. on day after last contact date)

[1] See Section 6.7 for definition of baseline, which will be used in the statistical analyses of safety laboratory data, ECG and vital signs.

Section 7.2.5 of the CTP: *Note that AEs occurring after the last per protocol contact but entered before final database lock will be reported to Pharmacovigilance only and will not be captured in the trial database.*

The following AE displays will be provided in the report:

1. In Section 15.3 and Appendix 16.1.13.1.8 (for ClinicalTrials.gov and EudraCT only), the on-treatment phase will be analysed (labelled with "short label"). Screening and follow-up periods will not be included in this analysis. The following totals will be provided in addition only in Section 15.3:
    - a total over all on treatment phases involving BI ("Total BI")
    - a total over all on treatment phases ("Total")
2. Section 15.4 of the CTR displays:
    - Screening
    - On-treatment (labelled with short labels defined in Table 6.1:2)
    - Follow-up (labelled "F/U")

3. Appendix 16.2 of CTR: all AEs will be listed.

Measurements will be considered on-treatment, if they were taken within the on-treatment phases as defined in Table 6.1: 2. For detailed information on the handling of the treatments refer to Technical TSAP ADS plan and Analysis Data Reviewers guide.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Consistency check listings (for identification of deviations from time windows) and a list of protocol deviations (e.g. deviations in drug administration, in blood sampling times, etc.) will be provided to be discussed at the Report Planning Meeting (RPM). At this meeting, it will be decided whether a discrepant data value can be used in analyses or whether it must be corrected in the clinical database. Each protocol deviation must be assessed to determine whether it is an important protocol deviation (iPD). For definition of iPDs, and for the process of identification of these, refer to the BI reference document "Identify and Manage Important Protocol Deviations (iPD)" (2).

If any iPDs are identified, they are to be summarised into categories and will be captured in the decision log. Categories which are considered to be iPDs in this trial are defined in the DV domain template and stored in TMF. If the data show other iPDs, the definition in the DV domain template
will be supplemented accordingly by the time of the RPM.

IPDs will be summarised and listed in the CTR. Which kind of iPDs could potentially lead to exclusion from which analysis set is specified in the DV domain template. The decision on exclusion of subjects from analysis sets will be made at the latest at the RPM, after discussion of exceptional cases and implications for analyses.

Non-important COVID-19 related PDs will only be listed.

6.3 SUBJECT SETS ANALYSED

The treated set (TS) and pharmacokinetic parameter analysis set (PKS) will be used as defined in the CTP, Section 7.3.

Section 7.3 of the CTP:

- *Treated set (TS): The treated set includes all subjects who were treated with at least one dose of trial drug. The treated set will be used for safety analyses.*

- *Pharmacokinetic parameter analysis set (PKS): This set includes all subjects in the treated set (TS) who provide at least one PK endpoint that was defined as primary or secondary and was not excluded due to a protocol violation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection 'Pharmacokinetics'). Thus, a subject will be included in the PKS, even if he contributes only one PK parameter value for one period to the statistical assessment. Descriptive and model based analyses of PK parameters will be based on the PKS.*

Section 7.3 of the CTP:

Plasma concentration data and parameters of a subject will be included in the statistical pharmacokinetic (PK) analyses if they are not flagged for exclusion due to a protocol deviation relevant to the evaluation of PK (to be decided no later than in the Report Planning Meeting) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Exclusion of a subject's data will be documented in the CTR.

Relevant protocol deviations may be

- *Incorrect trial medication taken, i.e. the subject received at least one dose of trial medication the subject was not assigned to*
- *Incorrect dose of trial medication taken*
- *Use of restricted medications*

Plasma concentrations and/or parameters of a subject will be considered as non-evaluable, if for example

- *The subject experienced emesis that occurred at or before two times median t_{max} of the respective treatment (Median t_{max} is to be determined excluding the subjects experiencing emesis),*
- *A predose concentration is >5% C_{max} value of that subject*
- *Missing samples/concentration data at important phases of PK disposition curve*

Plasma concentration data and parameters of a subject which is flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses. Descriptive and statistical models of PK parameters will be based on the PKS.

Only concentration values within the validated concentration range and actual sampling times will be used for the calculation of pharmacokinetic parameters. Concentrations used in the pharmacokinetic calculations will be in the same format provided in the bioanalytical report, (that is, to the same number of decimal places provided in the bioanalytical report).

Table 6.3: 1 Subject sets analyzed

	Subject set	
Class of endpoint	TS	PKS
Primary endpoint		X
Secondary PK endpoints		X
Further PK endpoints		X
Safety parameters	X	
Demographic/baseline characteristics	X	
Important protocol deviations	X	
Disposition	X	
Treatment exposure	X	

[redacted]

6.5 POOLING OF CENTRES

This section is not applicable, because the study was performed in only one centre.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Handling of missing data will be performed as described in the CTP section 7.5. Handling of missing PK data will be performed according to the relevant BI internal procedures. PK parameters that cannot be reasonably calculated based on the available drug concentration-time data will not be imputed.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

For each treatment period, the baseline value is defined as the last available off-treatment measurement before administration of BI 1810631 of the respective treatment period.

Section 6.1 of the CTP:

In period "NF fasted + rabeprazole", a time window of +/- 120 min around planned time applies to rabeprazole dosings in the mornings of Days -4 to -2. In that period, in the morning of Day -1, a time window of +/- 60 min around planned time applies to rabeprazole dosing.

In periods "TF1 fasted", "NF fasted", and "NF fed", a time window of +/- 180 min around planned time applies to procedures in the morning of Day -4.

On the evening of Day -1, a time window of +/- 180 min applies to the planned procedures; in any case admission is to be completed no later than 10 hours prior to BI 1810631 administration on Day 1.

For time windows before drug administration in the mornings of Days -4 to 1 refer to the Flow Chart.

The acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 30 min on Day 1 and ± 60 min on Day 2 if not specified otherwise in the Flow Chart.

For PK samples and other procedures starting from planned time of 46 hours (inclusive) after administration, a time window of +/- 120 minutes applies.

7. PLANNED ANALYSIS

Safety analysis (refer to Section 7.3.4) will be performed by [redacted] and will be presented in Sections 15.1 to 15.4 of the CTR and in Appendix 16.2 and 16.1.13.1.

Statistical model-based analysis of PK endpoints will be performed by BI and will be presented in Section 15.5 of the CTR and in Appendix 16.1.13.3.

Descriptive data analysis of PK endpoints and concentrations will be performed by the department of Translational Medicine and Clinical Pharmacology (TMCP) at BI and will be presented in Section 15.6 of the CTR and in Appendix 16.1.13.5.

The format of the listings and tables will follow the BI standards (see "Standards for Reporting of Clinical Trials and Project Summaries" (3)) with the exception of those generated for PK-calculations following BI standards for PK/PD analysis (4).

The individual values of all subjects will be listed, sorted by treatment sequence, subject number and visit, except for listings regarding PK, which will be sorted by treatment, subject number and planned time. The listings will be included in Appendix 16.2 and for PK in Appendix 16.1.13 of the CTR.

For end-of-text tables, the set of summary statistics for non-PK parameters is:

N	number non-missing observations
Mean	arithmetic mean
SD	standard deviation
Min	minimum
Median	median
Max	maximum

For analyte concentrations, the following descriptive statistics will additionally be calculated:

CV	arithmetic coefficient of variation
gMean	geometric mean
gCV	geometric coefficient of variation

For PK parameters, the following descriptive statistics will additionally be calculated:

P10	10th percentile
Q1	1st quartile
Q3	3rd quartile
P90	90th percentile

[redacted]

[redacted]

Main comparisons of interest

The main comparisons of interest in this trial to assess relative bioavailability are the following:

i. NF fasted (T1) versus TF1 fasted (R)
ii. NF fed (T2) versus NF fasted (T1)
iii. NF fasted + rabeprazole (T3) versus NF fasted (T1)

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the CTR.

The data will be summarised by treatment sequence and in total.

7.2 CONCOMITANT DISEASES AND MEDICATION

Descriptive statistics are planned for this section of the CTR.

Concomitant diseases and non-drug therapies will be coded according to the most recent version of the coding system of the Medical Dictionary for Drug Regulatory Activities (MedDRA). Concomitant medication will be coded according to the most recent version of the World Health Organization - Drug Dictionary (WHO-DD). The coding version number will be displayed as a footnote in the respective output.

In the remaining document ‘therapy’ will be used for non-drug therapies and concomitant medications.
The relevance of the concomitant therapies to the evaluation of PK will be decided no later than at the RPM.

Section 7.3.4 of the CTP:

Previous and concomitant therapies will be presented per treatment group without consideration of time intervals and treatment periods.

7.3 TREATMENT COMPLIANCE

Treatment compliance will not be analyzed or listed as a specific endpoint, but judged by observed analyte concentrations. Any deviation from complete food and medication intake will be addressed in the RPM (see Section 6.2) and described in the CTR.

7.4 PRIMARY ENDPOINT(S)

The following pharmacokinetic parameters will be determined for BI 1810631:

- $AUC_{0\text{-}tz}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point)
- C_{max} (maximum measured concentration of the analyte in plasma)

7.4.1 Primary analysis of the primary endpoint(s)

Section 7.3 of the CTP:

The pharmacokinetic parameters listed in Section 2.1 and 2.2.2 for drug BI 1810631 will be calculated according to the relevant BI internal procedures.

Section 7.3.1 of the CTP:

The statistical model used for the analysis of the primary endpoints will be an analysis of variance (ANOVA) model on the logarithmic scale. That is, the PK endpoints will be log-transformed (natural logarithm) prior to fitting the ANOVA model. This model will include effects accounting for the following sources of variation: sequence, subjects within sequences, period and treatment. The effect 'subjects within sequences' will be considered as random, whereas the other effects will be considered as fixed. The model is described by the following equation:

$y_{ijkm} = \mu + \zeta_i + s_{im} + \pi_j + \tau_k + e_{ijkm}$, *where*

y_{ijkm} = *logarithm of response measured on subject m in sequence i receiving treatment k in period j,*

μ = *the overall mean,*

ζ_i = *the* i^{th} *sequence effect, i = 1, 2, 3, 4*

s_{im} = *the effect associated with the* m^{th} *subject in the* i^{th} *sequence, m = 1, 2, ..,* n_i

π_j = *the* j^{th} *period effect, j = 1, 2, 3, 4*

τ_k = *the* k^{th} *treatment effect, k = 1, 2, 3, 4*

e_{ijkm} = the random error associated with the m^{th} subject in sequence i who received treatment k in period j.

where $s_{im} \sim N(0,\sigma_B^2)$ i.i.d., $e_{ijkm} \sim N(0,\sigma_W^2)$ i.i.d. and s_{im}, e_{ijkm} are independent random variables.

Point estimates for the ratios of the geometric means (T1/R, T2/T1 and T3/T1) for the primary endpoints (see Section 2.1) and their two-sided 90% confidence intervals (CIs) will be provided.

For each endpoint, the difference between the expected means for log(T1)-log(R), log(T2)-log(T1) and log(T3)-log(T1) will be estimated by the difference in the corresponding adjusted means (Least Squares Means). Additionally, their two-sided 90% confidence intervals will be calculated based on the residual error from the ANOVA and quantiles from the t-distribution. These quantities will then be back-transformed to the original scale to provide the point estimate and 90% CIs for each endpoint.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoint

This section is not applicable, as no key secondary endpoint has been specified in the protocol.

7.5.2 Secondary endpoints

Section 7.3.2 of the CTP:

The secondary endpoint … [$AUC_{0-\infty}$] will be calculated according to the BI internal procedures and will be assessed statistically using the same methods as described for the primary endpoints.

7.7 EXTENT OF EXPOSURE

Descriptive statistics of number of doses and calculated total dose are planned for this section of the CTR for both BI 1810631 and rabeprazole. The date and time of drug administrations will be listed for each subject.

7.8 SAFETY ANALYSIS

Section 7.3.4 of the CTP:

Safety will be analysed based on the assessments described in Section 2.2.2.2. All treated subjects (TS, refer to Section 7.2) will be included in the safety analysis. Safety analyses will be descriptive in nature and based on BI standards. No hypothesis testing is planned.

For all analyses, the treatment actually administered (= treatment at onset) to the subject will be used (any deviations from the randomised treatment will be discussed in the minutes of the Report Planning Meeting).

7.8.1 Adverse Events

AEs will be coded with the most recent version of MedDRA.

Unless otherwise specified, the analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the number of subjects with AEs and NOT on the number of AEs. BI standards as presented in "Analysis and Presentation of Adverse Event Data from Clinical Trials – Display Template" (5) and "Analysis and Presentation of AE data from clinical trials" (6) will be applied.

Section 5.2.6.1.4 of the CTP:

The following are considered as AESIs:
Potential severe DILI

A potential severe Drug Induced Liver Injury (DILI) that requires follow-up is defined by the following alterations of hepatic laboratory parameters:

- *An elevation of AST (aspartate transaminase) and/or ALT (alanine transaminase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or in samples drawn within 30 days of each other, or*

- *Aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN*

According to ICH E3 (7), in addition to deaths and serious adverse events, 'other significant' AEs need to be listed in the CTR. These will be any non-serious adverse event that led to an action taken with study drugs (e.g. discontinuation or dose reduced or interrupted).

The frequency of subjects with AEs will be summarised by treatment (see Table 6.1:2), primary system organ class (SOC) and preferred term (PT). Separate tables will be provided for subjects with serious AEs, for subjects with drug-related AEs, for subjects with drug-related serious AEs and for subjects with AESIs. In addition, the frequency of subjects with AEs will be summarised by treatment, maximum CTCAE grade, SOC and PT.
The SOCs and PTs within SOCs will be sorted by descending frequency over all treatment groups. The MedDRA version number will be displayed as a footnote in the respective output. AEs will be displayed by maximum CTCAE grade using the categorization "All grades", "Grade 1", "Grade 2", "Grade 3", "Grade 4" and "Grade 5".

For disclosure of AE data on ClinicalTrials.gov, the frequency of subjects with non-serious AEs that had an incidence of > 5% (in preferred terms) for at least one treatment and the frequency of subjects with SAEs will be summarised by treatment, primary SOC and PT. The frequency of all-cause mortality will be summarised by treatment.

For disclosure of AE data in the EudraCT register, the frequency of non-serious AEs (subjects and events) with an incidence of greater than 5% (in preferred terms), the frequency of SAEs (subjects and events) and the frequency of deaths (related or unrelated to SAEs) will be summarised by treatment, primary SOC and PT. The frequency of all-cause mortality will be summarised by treatment.

For support of lay summaries, the frequency of subjects with drug-related SAEs will be summarised by treatment, primary SOC and preferred term.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards "Handling, Display and Analysis of Laboratory Data" (8).

Analyses will be based on normalised values, which means transforming to a standard unit and a standard reference range. The original values will be analysed if the transformation into standard unit is not possible for a parameter.

Laboratory data will be analysed qualitatively via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as possibly clinically significant will be flagged in the data listings.

Clinically relevant findings in laboratory data will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analysed as such. It is the investigator's responsibility to decide whether a lab value is clinically significantly abnormal or not (at the RPM at the latest).

Descriptive statistics of laboratory data over time including change from baseline (see Section 6.7) will be calculated by planned time point based on the worst value of the subject at that planned time point (or assigned to that planned time point).

7.8.3 Vital signs

The analyses of vital signs (blood pressure and pulse rate) will be descriptive in nature. Descriptive statistics of vital signs over time and for the difference from baseline (see Section 6.7) will be provided.

7.8.4 ECG

ECG recordings will be checked by the investigator for pathological results. Clinically relevant abnormal findings for ECG will be listed under 'Relevant Medical History / Baseline Conditions' (when they occurred during screening) or will be reported as AEs (when they occurred during treatment), and will be analysed as such.

No separate ECG listing will be provided.

7.8.5 Others

7.8.5.1 Physical examination

Physical examination findings will be reported as relevant medical history/baseline condition (i.e., a condition already existent before intake of study drug) or as AE and will be summarised as such. No separate listing or analysis of physical examination findings will be prepared.

7.8.5.2 Body weight

Analysis of body weight at screening time point will be descriptive in nature.

7.8.6 Interim Analysis

Section 7.4 in CTP
No formal interim analysis is planned.

A preliminary, exploratory PK analysis of BI 1810631 and rabeprazole may be performedbased on evaluable data at any time prior to data base lock. This may be necessary, e.g. in case the information is needed to inform other activities during the development of BI1810631. In contrast to the final PK calculations, the preliminary, exploratory analysis will be based on planned sampling times rather than on actual times, regardless of whether actual times were within the time windows or not. Therefore, minor deviations of preliminary and final results may occur. No formal preliminary PK report will be written.

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

The treatment information will be loaded into the trial database after completion of enrolment, i.e. the randomization has been completed.

9. REFERENCES

1.	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
2.	*001-MCS-40-413:* "Identify and Manage Important Protocol Deviations (iPD)", current version, Group "Clinical Operations", IDEA for CON.
3.	*BI-KMED-BDS-HTG-0045:* "Standards for Reporting of Clinical Trials and Project Summaries", current version, Group "Clinical Trial Data Analysis", KMed.
4.	*BI-KMED-TMCP-MAN-0014*: "Noncompartmental Pharmacokinetic /Pharmacodynamic Analyses of Clinical Studies", current version, Group "TMCP Data Analysis", KMed.
5.	*BI-KMED-BDS-HTG-0041*: "Analysis and Presentation of AE data from clinical trials - display template", current version, Group "Clinical Trial Data Analysis", KMed.
6.	*BI-KMED-BDS-HTG-0066*: "Analysis and Presentation of AE data from clinical trials", current version, Group "Clinical Trial Data Analysis", KMed.
7.	*CPMP/ICH/137/95*: "Structure and Content of Clinical Study Reports", ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version, EMA webpage.
8.	*BI-KMED-BDS-HTG-0042*: "Handling, Display and Analysis of Laboratory Data", current version, Group "Clinical Trial Data Analysis", KMed.

11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1	**17-OCT-22**	[redacted]	None	This is the final TSAP